Patient preferences for topical treatment of actinic keratoses

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Patient preferences for topical treatment of actinic keratoses: a discrete-choice experiment

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Summary

Background

Treatment of actinic keratoses (AK) is a potentially effective strategy for prevention of cutaneous squamous cell carcinoma (cSCC). However, the patient perspective on potential benefits of AK treatment in terms of skin cancer reduction has received little attention to date.

Objectives

(1) To investigate patient preferences for AK topical treatments using a discrete choice experiment (DCE); (2) To evaluate patient willingness to trade between clinical benefit and medical burden.

Methods

The DCE was conducted as part of a study to establish the feasibility of a phase III RCT evaluating prevention of cSCC using currently available topical interventions. Preferences were elicited by asking patients to make a series of choices between treatment alternatives with different hypothetical combinations of attribute levels. Willingness to trade between treatment attributes was estimated using a flexible choice model that allows for the heterogeneity of patient preferences.

Results

109 patients with AK completed the DCE. The majority of patients who expressed valid preferences were willing to accept some reduction in both prophylactic and cosmetic efficacy to reduce the burden of the treatment regimen, the severity of skin reaction and other adverse effects. Patients may reject treatment if the perceived therapeutic benefit is outweighed by the subjective burden of treatment.

Conclusions

Evidence of significant variation in the perceived utility of treatments across patients highlights the importance of taking individual patient preferences into account to improve AK treatment acceptability and adherence.

What's already known about this topic?

- There are multiple therapies of varying efficacy licensed for the treatment of actinic keratoses (AK), but none yet proven to reduce skin cancer incidence.
- AK treatments all carry a therapeutic burden including pain, local skin inflammation and inconvenience of regimen.
- Discrete choice experiments (DCE) are increasingly used to elicit patient preferences and thereby improve adherence to treatment.

What does this study add?

- This is the first study to investigate patient willingness to undergo AK treatment using a discrete choice experiment.
- The majority of patients are able to discriminate between treatment characteristics and many of these patients are willing to make trade-offs between attributes.
- Patients are prepared to accept some reduction in efficacy in order to reduce treatment burden.

What are the clinical implications of the work?

- Treatment of AK is a potential strategy for skin cancer prevention, but is only feasible if patients are willing to consent and adhere to therapy.
- Knowledge of patient preferences will help to optimise the design of treatment protocols given that no currently available AK treatment is clearly superior in terms of both greater clinical benefit and reduced medical burden.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer in the UK, accounting for approximately 23% of the 132,000 new cases of non-melanoma skin cancer registered in 2014.[1,2] Cutaneous SCC incidence has more than doubled in the past 10 years and rates are predicted to continue rising with the increasing population of elderly individuals, placing a significant burden on health-care resources.[3] Ultraviolet radiation (UVR) is the principle environmental carcinogen and an estimated 23% of the UK population over 60 years have significant sun-damage and pre-cancerous skin lesions in the form of actinic keratoses (AK).[4] AK are considered to be precursor lesions for cSCC with a number of studies

demonstrating a close relationship between AK numbers and cSCC risk,[5,6,7] with 65% of cSCC arising from previously identified AK.[8] Treatment of AK might therefore provide an effective strategy for cSCC prevention, although this hypothesis has yet to be subjected to rigorous testing.[9,10]

AK can be individually treated with lesion-directed therapies such as surgery or cryotherapy, or a whole area of skin bearing multiple AK can be treated with field-directed therapy, which also aims to clear sub-clinical AK. A number of topical AK treatments with differing mechanisms of action are currently licensed in the UK for self-administration (e.g. diclofenac gel; 5-fluorouracil (5-FU) cream; imiquimod cream; ingenol mebutate gel). They vary in terms of therapeutic burden to patients (e.g. frequency of application, duration of treatment course, severity of local skin reactions and adverse effects), as well as their efficacy (i.e. proportion of AK cleared and persistence of clearance). For example, topical diclofenac 3% gel tends to cause fewer local skin reactions than 5-fluorouracil with salicylic acid, but treatment duration is longer and it is less effective in clearing AK.[9] Such factors may impact upon patient treatment preferences; understanding such preferences is important for improving acceptability of, and adherence to, these topical AK treatments.[11]

This study investigated patient preferences for topical AK treatments by means of a discrete choice experiment (DCE). DCEs are increasingly used in healthcare research to elicit patient preferences.[12] They are based upon the premise that medical treatments are characterised by a set of attributes and that the attractiveness of a specific treatment is a function of the levels of these attributes.[13] The relative importance of attributes is assessed by offering patients a series of choices between treatment alternatives that have different hypothetical combinations of attribute levels. This methodology has not previously been applied to understanding patient preferences in AK treatment.

Methods

Study design

Patients were presented with a series of choices between two hypothetical topical treatments for AK (A and B) and a 'no treatment' opt-out option in each choice set. The hypothetical nature of the treatments provided an opportunity to examine preferences across a wider range of attribute level combinations than exists in currently available treatments. Moreover, the true attribute levels of existing treatments do not need to be known to elicit patients' willingness to

trade between attributes. This willingness to trade was estimated using a flexible choice model that allows for the heterogeneity of respondents' preferences.

The selection of treatment attributes and levels is fundamental to obtaining valid DCE results.[13] In this study, an initial selection was made by one of the authors (CP) based upon review of the literature and expert knowledge from clinical practice. This initial selection was used in a pilot DCE administered to seven AK patients who subsequently participated in a focus group exploring their perspectives on the preliminary DCE design. The findings from this exercise were used to modify the initial choice of both attributes and associated levels, with Table 1 providing details of the final DCE design. Of the five attributes, three were associated with the *burden* of medication, (intensity and length of treatment, severity of local skin reaction, and occurrence of flu-like systemic side effects) and two with the *efficacy* of treatment (improvement in skin appearance and reduction in skin cancer risk). Attribute levels were chosen to be comparable, although not identical, with those of currently prescribed creams to ensure the clinical relevance of the results, with three levels specified for the reduction in skin cancer risk and two levels for the four other attributes.

Experimental design techniques[14, 15] were used to construct an orthogonal main effects plan consisting of 12 of the 48 possible combinations of treatment attributes and levels. To validate patient responses, a further two choice sets were added to the DCE: the first checked for rationality of patient choices by including a treatment with unambiguously higher levels of medical burden and lower levels of clinical efficacy; the second checked for consistency by including a treatment which was identical to one of the main choice sets, but with treatments A and B switched. The sequencing of the 14 choice sets was randomly generated for each individual patient questionnaire to mitigate against bias caused by learning or fatigue.[16]

Study sample and elicitation mode

The DCE was conducted as part of Skin cancer Prevention in Organ Transplant patients (SPOT), a multi-centre, randomised, 3-arm open-label phase II feasibility study comparing topical treatment of AK as a strategy for prevention of invasive cSCC.[17] Patients were recruited between December 2014 and June 2016, with organ transplant recipients (OTRs) recruited at Manchester Royal Infirmary, Royal Free Hospital London and Barts Health NHS Trust London, and immunocompetent patients (ICPs) at Churchill Hospital Oxford and Ninewells Hospital Dundee. Inclusion criteria were age 18 years and above; at least 10 AK occurring within the same or on adjacent body sites in immunosuppressed OTRs; and a past or current

history of AK in ICPs. The sample size *N* was determined by a power calculation for the main SPOT study, not the DCE, but the following rule of thumb[18, 19] was used to check that this would be adequate to detect the main effects in the choice model analysis:

$$N > (500 \times c)/(t \times a) = (500 \times 3)/(12 \times 3) = 41.7 \quad (1)$$

where *c=3* is the largest number of levels specified for any of the attributes (20%, 50% and 60% skin cancer risk reductions), *t=12* the number of choice sets or tasks utilised in the choice model analysis and *a=3* the number of alternatives in each task (A, B or no treatment).

The DCE formed part of a written questionnaire completed in clinic by patients before starting their randomised intervention (see Supplementary materials). Information collected included demographic data, history of skin problems including AK and previous treatments for AK. A detailed explanation of the DCE was provided to patients, with a trial clinician in attendance to answer queries. Patients were asked to report on their experience of completing the DCE.

Statistical analysis

Preference parameters were estimated based on a random utility model in which the utility or value that patient *i* assigns to treatment *j* in choice set *s*, U_{ijs}, is assumed to be the sum of a systematic component based on the attributes included in the DCE, and an error term ε_{ijs}:

$$U_{ijs} = \beta_{0i} + \sum_{k=1}^{K} \beta_{ki} A_{ijks} + \varepsilon_{ijs}; i = 1,\ldots n;\ j = 1,\ldots J; s = 1,\ldots S \quad (2)$$

where the treatment constant β_{0i} reflects the relative value of a treatment with maximum burden and minimum efficacy to no treatment at all, the utility weights β_{ik} (k=1,…K) indicate the importance of the attributes A_k relative to one another, and the absence of interaction terms between attributes is dictated by the DCE design. The preferred generalised multinomial logit (G-MNL) specification[20] takes preference heterogeneity into account by allowing both the treatment constant and the scale of the error term to vary randomly across patients. The model was estimated in Stata 14[21] by maximum simulated likelihood using 2000 Halton draws. Estimated utility weights were used to calculate patients' willingness to trade between treatment attributes on the assumption that the weights for both reductions in skin cancer risk and improvements in skin appearance are linear over the range of levels specified in the DCE.

Funding and ethics

SPOT is funded by the Research for Patient Benefit programme of the National Institute for Health Research. The study is approved by the Research Ethics Committees of the participating sites (EudraCT number 2013-000893-32) and all patients provided written informed consent.

Results

Sample characteristics

109 of 111 patients recruited into the SPOT study completed the DCE, of which 48 were OTRs and 61 were ICPs. Patient characteristics are summarised in Table 2. Patients were predominantly male with mean age 68 years (range 46 to 91 years). Most patients considered their AK to be moderately serious in nature, with over 70% selecting one of the three middle categories equating to moderately serious on a 7-point Likert scale. More than 80% of participants had received prior treatments for AK with more than half reporting previous use of a topical treatment, including 5-fluorouracil cream (48%), imiquimod cream (17%) and diclofenac gel (12%). As detailed in Table 2, there are a few significant differences between the OTR and ICP sub-populations, which include younger age of OTR and acral site of AK.

Patient preferences for treatment attributes

Figure 1 details the selection of the choice model sample by patient type. 25 respondents failed either one or both of the validity tests and were excluded from the subsequent DCE analysis. Patients were asked how difficult they found the DCE on a 5 point Likert scale (see supplementary Table 1), with a Mann-Whitney U test revealing that these patients found the DCE significantly more difficult to complete than those providing valid responses ($p<0.05$). A further 26 patients were classified as 'non-traders': they chose the option with the better level of one specific attribute (most commonly the hypothetical treatment with the higher level of cancer risk reduction – see supplementary Table 2) in all choice sets, revealing no willingness to trade between attributes at the levels specified in the study. The choices of these 26 patients are consistent with so-called 'lexicographic preferences' but not with the DCE methodology and they were therefore also excluded. The final choice model sample therefore comprised the 58 respondents with valid responses whose best option choices revealed that they were willing to trade between attributes. In the majority of cases (n=55) these respondents provided responses for all choice sets.

The choice model estimates are presented in Table 3. The signs of the estimated utility weights on all treatment attributes are consistent with *a priori* expectations, since positive values imply preferences for a lower medical burden and higher clinical efficacy. It follows that setting all attribute levels to zero will result in the worst possible hypothetical treatment option, one which has to be applied twice daily for 12 weeks, causes severe inflammation and systemic symptoms and results in only a moderate improvement in skin appearance and a 20% fall in the chance of developing skin cancer. The treatment constant provides a prediction of the mean expected utility value of this treatment option, with the positive value providing strong evidence ($p<0.01$) that it would be preferable to no treatment at all for the typical patient. Nevertheless, the estimate of the standard deviation of the treatment constant indicates significant preference heterogeneity, such that the expected utility value of the worst possible option will be negative – i.e. worse than no treatment at all – for about 0.3% of patients. The 'no treatment' option was chosen as the best option in six choice sets by one patient in the choice model sample. A Wald test failed to reject the linearity of utility weights over the range of skin cancer risk reductions included in the DCE ($p>0.10$), with the value of a change from a 20% to a 60% fall being insignificantly different from one third more than that of a change from a 20% to a 50% fall, holding all other attributes constant.

Trade-offs

Table 4 shows patients' willingness to trade between treatment attributes based on the estimated utility weights.[1] With respect to medical burden, patients place the highest value on a reduction in severity of the local skin reaction (from severe to mild), followed by the length and intensity of the treatment regimen (from twice daily for 12 weeks to daily for a week) and finally the elimination of flu-like systemic symptoms. Patients are willing to accept increases in the risk of developing skin cancer of 13.4, 9.7 and 6.7 percentage points respectively – or forgo improvements in skin appearance of 37.0, 26.9 and 18.5 percentage points – in order to mitigate these three aspects of treatment burden. Patients value changes in skin cancer risk more highly than in cosmetic outcome, being prepared to accept a 0.36 percentage point increase in the risk of developing skin cancer to obtain a 1 percentage point improvement in skin appearance.

[1] Given the linearity assumption, the implied utility weights for a 1% reduction in skin cancer risk and 1% improvement in skin appearance are respectively 0.056 = (1.756/30+2.142/40)/2 and 0.020 = 1.016/50.

Discussion

Keratinocyte skin cancers are increasingly common creating both health burden and expense in our ageing population. They are especially burdensome in immunosuppressed patients, such as OTRs, who have an approximately 100-fold increased risk of developing cSCC and accelerated progression from AK to cSCC.[22] Prevention of cSCC through systematic targeting of the common and visible precursor, AK, sounds logical, but is only feasible if effective treatments are acceptable to the patient population needing to use them. Previous studies of topical AK treatments have included patient reported outcomes as secondary outcomes, including patients' tolerance of the regimen, satisfaction with the cosmetic appearance and choice of future treatment. This is the first study, however, to systematically explore patient preferences for AK treatments using a DCE designed to investigate their willingness to undergo treatment and, if so, to trade between different treatment attributes. Understanding these preferences will help health professionals and decision-makers to optimise the design of treatment protocols for AK. This is a live issue since there is no currently available treatment that is clearly superior with respect to acceptability, efficacy and subsequent reduction in skin cancer risk. For example, Stockfleth et al.[9] find that 5-fluorouracil cream is more clinically effective than diclofenac gel, but it is less well tolerated with a higher proportion of patients reporting local adverse reactions. In this DCE study we have shown that the majority of patients are able to discriminate between treatment attributes showing specific preferences that can be incorporated into future strategies to improve adherence.

Our results are consistent with *a priori* expectations in that patients overwhelmingly express preferences for lower treatment burden and higher clinical efficacy. Our results also show that nearly 70% of patients who expressed valid preferences revealed a willingness to make trade-offs between attributes in their treatment option choices. The remainder based their best option choices on the better level of one specific attribute only and for roughly half of these patients, in both the OTR and ICP sub-samples, this single factor was a greater reduction in skin cancer risk. The apparent strength of preferences among this sub-set of non-traders, even if they are the result of heuristic decision-making,[23] may be taken as an indication that they would be almost certain to accept treatment irrespective of the severity of the treatment burden.

The choice model estimates imply that patients who are willing to trade between attributes would accept some reduction in both the prophylactic and cosmetic benefit of

treatment in order to reduce the length and intensity of treatment regimens, pain and skin inflammation due to local adverse reactions, and the incidence of other side effects. Patients' preferences may be influenced by length of treatment course, as in preference for photodynamic therapy,[10] and/or by local (and systemic) adverse events with skin inflammation being a frequent complication of topical treatments for AK.[24] In this DCE study, the hypothetical attribute levels were chosen so as to provide health professionals with relevant information to make clinical decisions that reflect patient preferences between currently licenced topical treatments.

The choice model estimates also demonstrate significant variation in the value that individual patients place on treatment options, although even the worst possible hypothetical treatment (high medical burden with low clinical efficacy) was preferable to no treatment for virtually all patients. Nevertheless, a very small proportion of patients might be expected to reject such an option, with one participant choosing no treatment as the best option in a number of the choice sets presented in the DCE. Serra-Guillen et al.[25] report that only 70% of patients treated with imiquimod would be willing to repeat the treatment. Moreover, patients who are prepared to accept treatment but do not value it highly might be less likely to adhere to the regimen. The clinical importance of non-adherence has been highlighted in the most recent Cochrane review on AK treatment.[24]

Our study has several potential limitations. First, although the design of the DCE was based on expert opinion and further refined by results of a pilot exercise, it is possible that we did not include all attributes that are relevant to patient preferences for AK treatment. Second, respondents may have been unfamiliar with different AK treatments or did not fully understand the nature of the choices that they were being asked to make. However, most respondents had previously received AK treatments – and over half had experienced a topical treatment – with hypothetical attribute levels chosen to be comparable with those of the currently prescribed agents. Moreover, the DCE was completed in clinic with a research nurse in attendance to check on the respondent's understanding. Third, the DCE design allowed only for main effects and we were therefore unable to identify any specific effects associated with particular combinations of attribute levels. Previous research has found that main effects typically account for the bulk of the variation in a DCE with interactions playing a smaller role.[26] Fourth, the sample size was determined by a power calculation for the main SPOT study, not the DCE, but an established rule of thumb[18, 19] indicated that the choice model sample was more than adequate to detect the main effects. Fifth, the results may be sensitive to the choice model

specification. However, a robustness analysis produced virtually identical findings across a range of alternative logit model specifications (see supplementary Table 3). Finally, our findings are based on a sample of patients recruited from specialist clinics in a single country (UK) and may not necessarily be generalisable to treatment of AK in other settings. Preferences for attributes/levels may differ according to a number of factors including age, sex, education, patient type and prior medical history including previous AK treatments, but we were not able to reliably demonstrate evidence of significant differences in treatment valuations between patients with different observable characteristics given the limited sample size. Overall, however, we believe the clinical setting and patient characteristics are representative of current AK treatment practice in secondary care in the United Kingdom.

Conclusion

This study demonstrated that patients may reject an AK treatment if the perceived value of the therapeutic benefits is outweighed by the subjective costs associated with the medical burden. Moreover, most patients would be prepared to accept some reduction in both the prophylactic and therapeutic efficacy of treatment in order to reduce the length and intensity of the regimen, and local or systemic symptoms including skin inflammation and pain. This will impact the feasibility of skin cancer prevention strategies that include AK treatments. Evidence of significant variation in the perceived utility of treatments between patients highlights the importance of taking individual patient preferences into consideration as part of clinical decision-making in order to improve adherence to topical AK treatments.

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Figure 1. DCE Study Flow Diagram

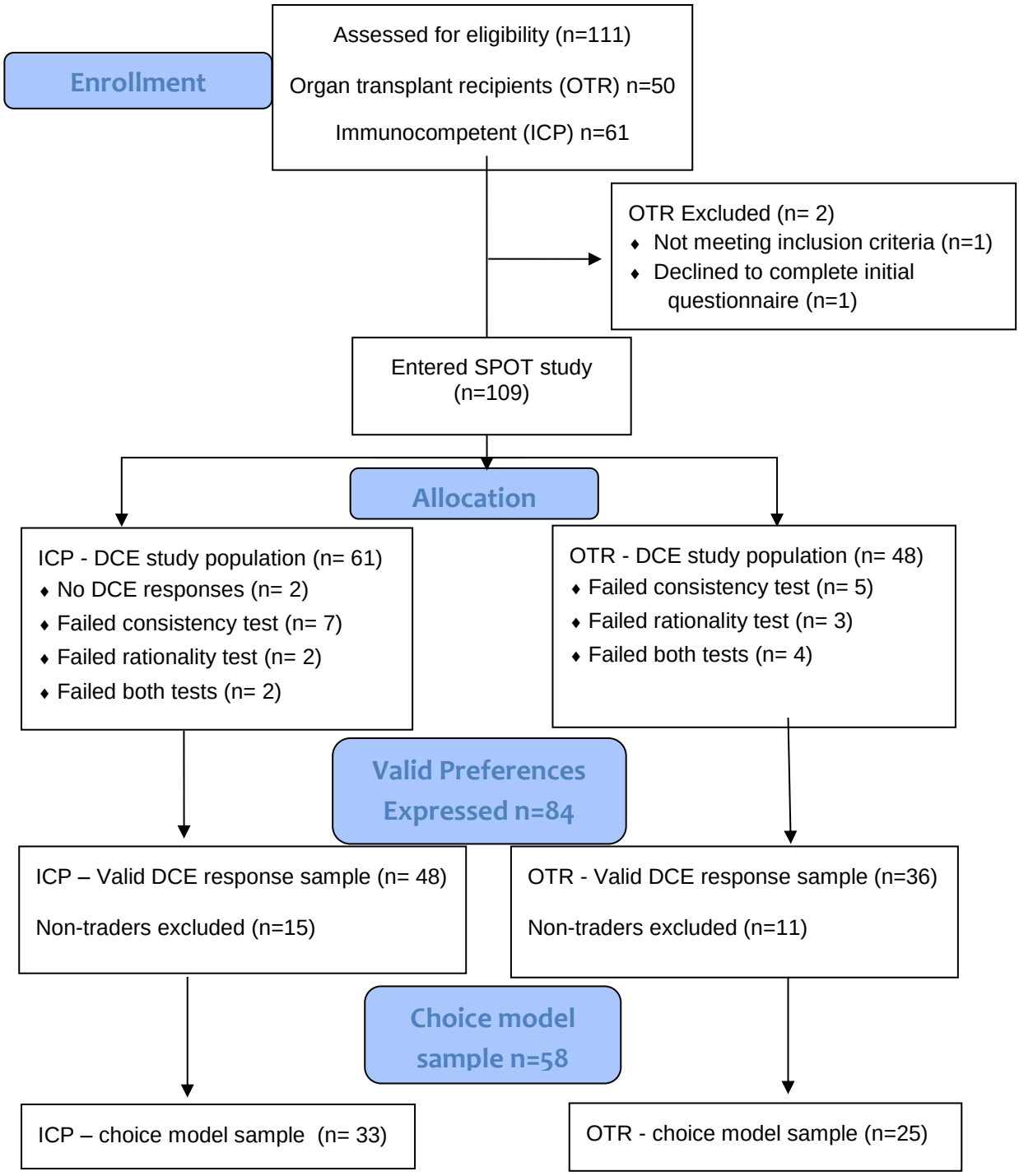


Table 1. Attributes and levels for hypothetical AK treatments

Attribute	*Level*	
Intensity and length of treatment	*1*	*Daily for 1 week*
	0	*Twice daily for 12 weeks*
Severity of reaction	*1*	*Mild inflammation with some discomfort*
	0	*Severe inflammation with moderate pain*
Other side effects	*1*	*No other side effects*
	0	*Flu-like symptoms, such as fever, fatigue, headache, nausea, diarrhoea and muscle pain*
Improvement in skin appearance	*0*	*Moderate improvement with 50% clearance of AK skin lesions*
	1	*Big improvement with 100% clearance of AK skin lesions*
Reduction in risk of skin cancer	*0*	*20%*
	1	*50%*
	2	*60%*

Table 2: Patient characteristics

Patient Characteristic	DCE study population (n=109)	OTR - DCE study population (n=48)	ICP - DCE study population (n=61)
Age	69.63 [45.83-90.89]	65.72* [45.83-82.44]	72.69* [50.45-90.89]
Male	78.90% (86)	81.25% (39)	77.05% (47)
Organ transplant recipient	44.04% (48)	100.0% (48)	0.00% (0)
Age first left education			
16 years or less	46.79% (51)	41.67% (20)	50.82% (31)
17-19 years old	23.85% (26)	29.17% (14)	19.67% (12)
20 years or over	28.44% (31)	27.08% (13)	29.51% (18)
Not supplied	0.92% (1)	2.08% (1)	0.00% (0)
Time since most recent diagnosis			
Less than 1 day	1.83% (2)	0.00% (0)	3.28% (2)
Less than 3 months	1.83% (2)	2.08% (1)	1.64% (1)
Between 3 months and 1 year	8.26% (9)	8.33% (4)	8.20% (5)
Between 1 and 3 years	14.68% (16)	10.42% (5)	18.03% (11)
Between 3 and 10 years	34.86% (38)	35.42% (17)	34.43% (21)
More than 10 years	37.61% (41)	41.67% (20)	34.43% (21)
Not supplied	0.92% (1)	2.08% (1)	0.00% (0)
Areas affected by AK			
Number of areas affected	4.23 [1-12]	4.65 [1-12]	3.90 [1-11]
Face	63.30% (69)	70.83% (34)	57.38% (35)
Nose	38.53% (42)	35.42% (17)	40.98% (25)
Forehead	46.79% (51)	45.83% (22)	47.54% (29)
Scalp	51.38% (56)	56.25% (27)	47.54% (29)
Ears	34.86% (38)	37.50% (18)	32.79% (20)
Hands	48.62% (53)	64.58%* (31)	36.07%* (22)
Arms	38.53% (42)	50.00%* (24)	29.51%* (18)
Legs	27.52% (30)	29.17% (14)	26.23% (16)
Feet	6.42% (7)	10.42% (5)	3.28% (2)
Neck	22.94% (25)	20.83% (10)	24.59% (15)
Chest	22.02% (24)	20.83% (10)	22.95% (14)
Back	20.18% (22)	20.83% (10)	19.67% (12)
Other	1.83% (2)	2.08% (1)	1.64% (1)
Self-rated seriousness of AK condition			
1. Not serious	7.41% (8)	2.13% (1)	11.48% (7)
2	16.67% (18)	8.51%* (4)	22.95%* (14)
3	25.00% (27)	36.17%* (17)	16.39%* (10)
4. Moderately serious	25.00% (27)	25.53% (12)	24.59% (15)
5	17.59% (19)	17.02% (8)	18.03% (11)
6	4.63% (5)	6.38% (3)	3.28% (2)
7. Very serious	3.70% (4)	4.26% (2)	3.28% (2)
Received previous treatment for AK	83.49% (91)	83.33% (40)	83.61% (51)
Past cryotherapy	57.80% (63)	64.58% (31)	52.46% (32)
Past photodynamic therapy	10.09% (11)	10.42% (5)	9.84% (6)
Past Diclofenac (Solaraze®) gel	11.93% (13)	10.42% (5)	13.11% (8)
Past skin surgery	42.20% (46)	41.67% (20)	42.62% (26)
Past 5-fluorouracil (Efudix®) cream	47.71% (52)	43.75% (21)	50.82% (31)
Past imiquimod (Aldara®) cream	16.51% (18)	20.83% (10)	13.11% (8)
Past other treatment	9.17% (10)	10.42% (5)	8.20% (5)
Does not remember past treatment	4.59% (5)	6.25% (3)	3.28% (2)
DCE difficulty (5=highest)	2.73 [1-5]	2.79 [1-4]	2.68 [1-5]

Notes: Continuous variables show mean and range [in square brackets].
Dummy variables show percentage and number (in brackets).
* Indicates a statistically significant difference between the OTR and ICP samples at the 5% level.

Table 3: Generalised multinomial logit (G-MNL) model estimation results

	Coefficient estimate [95% Confidence interval]
Attributes	
Regimen: (reference level twice daily for 12 weeks)	
Daily for 1 week	0.546*** [0.217,0.875]
Local skin reaction: (reference level severe)	
Mild	0.751*** [0.359,1.142]
Systemic effects: (reference level flu-like symptoms)	
No other side effects	0.376** [0.059,0.692]
Skin appearance: (reference level moderate improvement)	
Big improvement	1.016*** [0.582,1.450]
Cancer risk: (reference level 20% fall)	
50% fall	1.756*** [0.786,2.725]
60% fall	2.142*** [0.933,3.352]
Treatment constant	
Mean	11.590*** [4.778,18.400]
Standard deviation	4.229*** [2.221,6.236]
Scale heterogeneity parameter	0.657** [0.128,1.185]

Number of observations 2076 (58 respondents × 12 choices, minus 12 missing values).
Log-likelihood = -346.1.
Akaike information criterion = 710.2. Bayesian information criterion 761.0.
* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 4: Estimates of Willingness to Trade Treatment Burden for Clinical efficacy

Attributes	Worse cosmetic outcome	Higher skin cancer risk
	Percentage points	*Percentage points*
Regimen: (reference level twice daily for 12 week)		
Daily for 1 week	26.9** [11.2– 42.5]	9.7** [3.1–16.4]
Local skin reaction: (reference level severe)		
Mild	37.0** [19.6– 54.3]	13.4** [5.3–21.5]
Systemic effects: (reference level flu-like symptoms)		
No other side effects	18.5* [1.4– 35.6]	6.7* [1.7–11.7]
Skin appearance		
1 percentage point improvement		0.36** [0.23– 0.50]

Estimates presented as mean [95% confidence interval]. A positive willingness to pay means that patients are willing to trade a reduction in medical efficacy for the specified level or improvement in the attribute. * $p < 0.05$, ** $p < 0.01$

Supplementary material: Introduction to DCE

Long Q

Part III: TOPICAL TREATMENT CHOICES

INTRODUCTION

In this part of the questionnaire, you will be asked to choose between various skin creams for the topical treatment of your AK skin lesions. The responses you give will help us find out about the acceptability to patients of alternative skin creams for the topical treatment of AK skin lesions and prevention of skin cancers. The information you provide will be completely confidential and will not affect the treatment you may actually receive in any way.

You will be presented with 14 questions in total relating to different skin cancer prevention treatments.. In each question, you are asked to choose between three treatment options: Treatment with skin cream A (Treatment A), Treatment with skin cream B (Treatment B) and No treatment.

To help you make these choices we will first describe how the treatment options can differ from each other. The treatments that you will be asked to choose between will vary in terms of:

how often the cream is applied and how long the course of treatment lasts,

how severe the skin reaction is during the treatment,

whether there are other side-effects of treatment,

how much the skin appearance improves as a result of the treatment and

how much the treatment reduces your risk of developing skin cancer.

On the following pages, we will look at each of these treatment attributes in detail.

We will then explain how we would like you to answer the questions.

Please continue on the next page

Intensity and length of treatment:

Treatments A and B must be applied as follows:

Daily for 1 week	Twice daily for 12 weeks

The "No treatment" option will always involve no applications of cream.

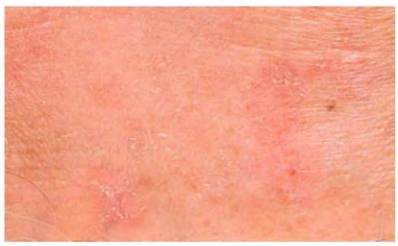
Severity of reaction:

Skin creams A and B will have one of the following severities of reaction during the course of treatment:

Mild inflammation with some discomfort	Severe inflammation with moderate pain
	

The "No treatment" option will always cause no reaction:

No reaction



Please continue on the next page

Other Side effects:

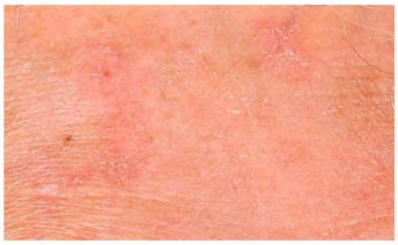
Skin creams A and B will also either cause flu-like symptoms or have no other side effects during the course of treatment:

Flu-like symptoms, such as fever, fatigue, headache, nausea, diarrhoea and muscle pain	No other side effects

The "No treatment" option will always cause no side effects.

Improvement in skin appearance:

Treatment with skin creams A and B will have one of the following effects on appearance:

Moderate improvement with 50% clearance of AK skin lesions 	Big improvement with 100% clearance of AK skin lesions 

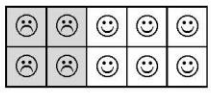
The "no treatment" option will always have little or no effect on your appearance with less than 10% clearance of AK skin lesions".

No improvement

Please continue on the next page

Reduction in risk of skin cancer:

Treatment with skin creams A and B will have one of the following effects on one's risk of developing skin cancer:

Your chance of developing skin cancer falls (is reduced) by 20%, i.e. out of 10 people who would have gone on to develop skin cancer, now only 8 will do so.	Your chance of developing skin cancer falls (is reduced) by 50%, i.e. out of 10 people who would have gone on to develop skin cancer, now only 5 will do so.	Your chance of developing skin cancer falls (is reduced) by 60%, i.e. out of 10 people who would have gone on to develop skin cancer, now only 4 will do so.
		

The "no treatment" option will always have no effect on your chance of developing skin cancer.

No change


HOW TO ANSWER THE QUESTIONS

When answering these questions, we would like you to imagine that your dermatologist is offering you the choice of treatment options (Treatment A, Treatment B, No treatment) and that (s)he would like you to pick the options that you most and least prefer. You would do this by putting a tick in appropriate boxes.

Please note that many of the treatment options that are presented in this part of the questionnaire are purely hypothetical choices that could not in practice be made available to you by your doctor.

When making your choice, please assume that the treatment options are similar in all respects other than in terms of the treatment attributes described above.

Please refer to the preceding information about treatment attributes, if you need help to make your decisions.

Please remember, **there are no right or wrong answers**.

We just want to know what **YOU** think.

Please continue on the next page

Here is an **EXAMPLE QUESTION** to help you answer the questions that follow:

Example question

	Treatment A	Treatment B	No treatment
The treatment must be applied	daily for 1 week	twice daily for 12 weeks	no applications
Your reaction to the course of treatment will be	mild inflammation with some discomfort 	severe inflammation with moderate pain 	no reaction 
During the course of treatment you will also experience	flu-like symptoms	no other side effects	no side effects
As a result of the treatment your appearance will show	moderate improvement (50% AKs clearance) 	big improvement (100% AKs clearance) 	no improvement 
As a result of the treatment your chance of developing skin cancer will	fall by 20% 	fall by 60% 	not change 
Which option do you think is the best? (Please tick one box)	☑ Option A	☐ Option B	☐ No treatment
Which option do you think is the worst? (Please tick one box)	☐ Option A	☐ Option B	☑ No treatment

IN THIS CASE YOU WOULD MOST PREFER TO:

Have the option of a treatment requiring daily application for 1 week of a cream that results in a mild skin reaction and flu-like symptoms during the course of the treatment. The treatment would produce a moderate improvement in appearance but would result in only a limited reduction in your risk of potentially developing skin cancer.

AND YOU WOULD LEAST PREFER TO:

Have no treatment at all. With no applications of cream you would have no skin reaction and no side effects, but little or no improvement in skin appearance and also no reduction in your risk of potentially developing skin cancer.

Please continue on the next page

Supplementary Table 1: Difficulty with DCE completion by subgroup

	Very easy	Rather easy	Neither easy nor difficult	Rather difficult	Very difficult	Total
Invalid DCE response subgroup	3	2	9	9	1	24
Non-trader subgroup	4	11	8	2	1	26
Final DCE analysis subgroup	6	18	23	9	2	58
DCE study population	13	31	40	20	4	108

Notes: One participant in the invalid DCE response subgroup did not answer the question.

Supplementary Table 2: 'Non-trader' Choices by Patient Type and Dominant Attribute

	Proportion of 'non-traders' in valid sample (absolute number in brackets)		
Dominant attribute	OTR patients	ICP patients	2-way t test p value
Intensity and length of treatment	0.0% (0)	8.3% (4)	0.078*
Severity of reaction	5.6% (2)	2.1% (1)	0.402
Other side effects	5.6% (2)	2.1% (1)	0.402
Improvement in skin appearance	5.6% (2)	4.2% (2)	0.771
Reduction in risk of skin cancer	13.9% (5)	14.6% (7)	0.929
Total	30.1% (11)	31.3% (15)	0.947

Notes: * $p < 0.10$. 'Non-traders' chose the option with the better level of one specific attribute in all choice sets, ignoring all other differences between the alternatives.

Supplementary Table 3: Alternative choice model estimation results

The Table below presents the choice model estimates for each of the logit specifications considered in the study. Column 1 reports the results for a basic multinomial logit (MNL) model specification. The mixed logit (MIXL) specification in column 2 allows the treatment constant, and thereby the mean value of treatments, to vary randomly across all participants. The scaled multinomial logit (S-MNL) specification in column 3 captures preference heterogeneity for individual treatment attributes by allowing the standard deviation of the idiosyncratic error term to vary randomly across participants. Our preferred generalised multinomial logit (G-MNL) model specification in column 4 allows for both sources of random preference heterogeneity. The reported log likelihood and information criteria indicate that all three variants are superior to the basic MNL specification, with the G-MNL model chosen on this basis and the statistical significance of both random preference heterogeneity parameters. Attempts to allow for heterogeneous preferences due to observable patient characteristics failed due to the sparseness of the data,[1] with the 'no treatment' option only chosen by one patient in six choice sets. Finally, the rank-ordered logit (ROL) specification in column 5 is based on that of the MNL model, but estimation of the utility weights makes use of the sample information on both best and worst option choices. A Hausman test failed to reject the null hypothesis that the same utility weights were applied in making both choices ($p>0.10$).

Supplementary references

1. Hosmeer DW, Lemeshow S and Sturdivant RX. Applied Logistic regression, 3rd Edition. New Jersey: Wiley, 2013.

	1 MNL	2 MIXL	3 S-MNL	4 G-MNL	5 ROL
Attribute					
Regimen: (reference level twice daily for 12 weeks)					
Daily for 1 week	0.466***	0.468***	0.577***	0.546***	0.452***
	[0.258,0.674]	[0.260,0.677]	[0.215,0.939]	[0.217,0.875]	[0.247,0.658]
Skin reaction: (reference level severe)					
Mild	0.642***	0.645***	0.794***	0.751***	0.606***
	[0.429,0.855]	[0.431,0.860]	[0.346,1.243]	[0.359,1.142]	[0.396,0.816]
Other side effects: (reference level flu-like symptoms)					
No other side effects	0.337***	0.338***	0.376**	0.376**	0.337***
	[0.133,0.541]	[0.133,0.543]	[0.036,0.715]	[0.059,0.692]	[0.147,0.527]
Appearance: (reference level moderate improvement)					
Big improvement	0.844***	0.847***	1.053***	1.016***	0.783***
	[0.638,1.050]	[0.640,1.054]	[0.629,1.476]	[0.582,1.450]	[0.577,0.988]
Cancer risk: (reference level 20% fall)					
50% fall	1.330***	1.334***	1.817***	1.756***	1.297***
	[0.980,1.681]	[0.981,1.686]	[0.947,2.688]	[0.786,2.725]	[0.982,1.612]
60% fall	1.595***	1.602***	2.230***	2.142***	1.523***
	[1.198,1.993]	[1.203,2.000]	[1.147,3.314]	[0.933,3.352]	[1.134,1.912]
Treatment constant					
Mean	2.053**	19.380*	2.241**	11.590***	2.911***
	[0.068,4.039]	[-1.892,40.649]	[0.216,4.265]	[4.778,18.400]	[1.644,4.177]
Standard deviation	~	8.930**	~	4.229***	~
		[1.078,16.781]		[2.221,6.236]	
Scale heterogeneity parameter	~	~	0.733***	0.657**	~
			[0.323,1.142]	[0.128,1.185]	
Observations	2076	2076	2076	2076	2076
Individuals	58	58	58	58	58
Log-likelihood	-367.2	-347.5	-361.0	-346.1	-429.1
Akaike Information Criteria	748.4	711.1	737.9	710.2	872.3
Bayesian Information Criteria	787.9	756.2	783.0	761.0	911.7
Hausman test (p value)	~	~	~	~	0.254

95% confidence interval in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$